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Registration Decision RD2012-01

Prothioconazole

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Registration Decision for Prothioconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Prothioconazole Technical Fungicide and JAU6476 100FS Seed Treatment Fungicide, containing the technical grade active ingredient prothioconazole, and L1397 Seed Treatment Fungicide, containing the technical grade active ingredients prothioconazole, metalaxyl and tebuconazole, to control seed and seedling diseases of various crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were proposed for full registration in the consultation document[1] Proposed Registration Decision PRD2011-07, *Prothioconazole*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for prothioconazole and summarizes the Agency's decision and the reasons for it. The PMRA received no comments on PRD2011-07. This decision is consistent with the proposed registration decision stated in PRD2011-07.

For more details on the information presented in this Registration Decision, please refer to PRD2011-07, which contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Prothioconazole?

The active ingredient prothioconazole and the associated end-use product JAU6476 100FS Seed Treatment belong to a major class of sterol biosynthesis inhibitor fungicides called demethylation inhibitors. Demethylation inhibitor fungicides are classified as Group 3 fungicides. JAU6476 100FS Seed Treatment is a seed treatment fungicide for use on corn, small-grain cereals, large-seeded pulse crops and soybean.

L1397 Seed Treatment Fungicide is a seed treatment fungicide formulation containing prothioconazole, tebuconazole and metalaxyl. Prothioconazole and tebuconazole are demethylation inhibitor fungicides. Metalaxyl belongs to the phenylamide class of fungicides and is classified as a Group 4 fungicide. L1397 Seed Treatment Fungicide is for use on small-grain cereals.

Health Considerations

Can Approved Uses of Prothioconazole Affect Human Health?

Potential exposure to prothioconazole and its prothioconazole-desthio metabolite may occur through the diet (food and water) or when handling and applying the product. Prothioconazole and prothioconazole-desthio have a similar toxicological profile with prothioconazole-desthio effects occurring at lower doses. Therefore, the endpoints used for this risk assessment were those of the metabolite. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when prothioconazole (with prothioconazole-desthio) products are used according to label directions.

Prothioconazole and prothioconazole-desthio were considered to be of low acute toxicity by the oral, dermal and inhalation routes in Wistar rats. These compounds were non-irritating when applied to the skin of rabbits. Prothioconazole was considered slightly irritating to the eyes of rabbits while prothioconazole-desthio was non-irritating. The results of skin sensitization testing were negative for both compounds, as such, no signal words are required on the label.

The end-use product JAU6476 100FS Seed Treatment Fungicide is of low acute toxicity to rats via the oral, dermal, and inhalation routes. It is non-irritating to the eye and slightly irritating to the skin of rabbits. JAU6476 100FS Seed Treatment Fungicide caused an allergic skin reaction.

The end-use product L1397 Seed Treatment Fungicide is of low toxicity to rats via the oral, dermal, and inhalation routes. It is moderately irritating to the eye and non-irritating to the skin of rabbits. It did not cause an allergic skin reaction.

Prothioconazole and prothioconazole-desthio did not cause cancer in animals and were not genotoxic. Decreased motor and locomotor activity were observed following dosing with these compounds. Numerous reproductive effects were also observed. The first signs of toxicity in animals given daily doses of these compounds over longer periods of time were liver, kidney, thyroid and ovary effects. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When prothioconazole was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to this compound than the adult animal. When prothioconazole-desthio was given to pregnant animals, effects on the developing fetus were observed at doses that were not toxic to the mother, indicating that the fetus is more sensitive to this compound than the adult animal. Because of this observation, extra protective measures were applied during the risk assessment to further reduce the allowable level of human exposure to prothioconazole-desthio.

Residues in Water and Food

Aggregate dietary intake estimates (food plus water) revealed that females 13-49 years old, the most sensitive population group to prothioconazole, are expected to be exposed to less than 33% of the acceptable daily intake, and all infants (<1 year), the population group that would ingest the most prothioconazole relative to body weight, are expected to be exposed to ≤20% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from prothioconazole is not of concern for all segments of the population. There is no evidence that prothioconazole is carcinogenic; therefore, a cancer dietary exposure assessment was not required.

A single dose of prothioconazole is not likely to cause acute health effects in the general population (including infants and children). An aggregate (food and water) dietary intake estimate for females 13-49 years old was less than 84% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue at the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using prothioconazole on various crops were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

Occupational Risks From Handling JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide

Occupational risks are not of concern when JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide are used according to the proposed label directions, which include protective measures.

Seed treatment workers in commercial seed treatment facilities or on-farm, who treat seeds with JAU6476 100FS Seed Treatment Fungicide or L1397 Seed Treatment Fungicide, as well as workers planting treated seed, can come in direct contact with prothioconazole residues on the skin. Therefore, the label specifies that during seed treatment, workers must wear long pants, a long-sleeved shirt and chemical resistant gloves. In addition, workers bagging treated seed, handling bagged seed or transferring treated seed to a storage bin must also wear a dust mask. Workers planting treated seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves when handling treated seed. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for seed treatment workers and planters, the risks to these individuals are not of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Prothioconazole Is Introduced Into the Environment?

Environmental risks to non-target organisms are not of concern when JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide are used according to label directions, which include a precautionary label statement.

Prothioconazole and the transformation products prothioconazole-desthio and prothioconazole-*S*-methyl have been considered together in a total toxic residue approach. Total toxic residues of prothioconazole are not expected to persist in soil, nor are they expected to carryover to the next growing season.

These compounds have low potential to leach through the soil profile and enter groundwater. Total toxic residues of prothioconazole are not expected to persist in aquatic environments under aerobic conditions, but they are expected to be persistent under anaerobic conditions. Residues of prothioconazole are not expected to be present in air due to its low volatility.

JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide, when used according to label directions, do not present a risk to earthworms, bees, beneficial arthropods and other insects, terrestrial plants and aquatic organisms. The overall risk to birds and mammals from the consumption of seeds treated with JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide is considered to be low. No mitigation measures are required, other than a precautionary label statement to clean up spilled seeds, and an advisory statement to identify the leaching potential of metalaxyl, one of the active ingredients in L1397 Seed Treatment Fungicide.

Value Considerations

What Is the Value of JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide?

JAU6476 100FS Seed Treatment Fungicide is a broad-spectrum systemic fungicide that contains prothioconazole, a new seed treatment active ingredient that can be used in an integrated pest management program for seed and seedling diseases of small-grain cereals, corn, soybean, dry pea, lentil, and chickpea. This will contribute to reduce resistance development in fungal populations which is already considered low for seed treatment.

L1397 Seed Treatment Fungicide contains prothioconazole as well as metalaxyl and tebuconazole. This seed treatment is for use on small-grain cereals.

As seed treatments, the rate per hectare of both of these products is low and application to the seed reduces exposure to non-target organisms compared to foliar pesticide applications. In addition to reducing resistance development and exposure to non-target organisms, these two end-use products will provide an additional tool to growers for control and suppression of a wide range of seed and seedling diseases on important Canadian crops.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the labels of JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with JAU6476 100FS Seed Treatment Fungicide and L1397 Seed Treatment Fungicide on the skin or through inhalation, anyone treating seed, or handling seed treated with JAU6476 100FS Seed Treatment Fungicide or L1397 Seed Treatment Fungicide must wear long pants, a long-sleeved shirt and chemical resistant gloves. In addition, workers bagging treated seed, handling bagged seed or transferring treated seed to a storage bin must also wear a dust-mask. Workers planting treated seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves when handling treated seed.

Environment

Precautionary label statements to clean up spilled seeds are included on the labels. An advisory label statement is required on the label for L1397 Seed Treatment Fungicide to reduce potential leaching to groundwater of metalaxyl, one of the active ingredients in this end-use product.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2011-07, *Prothioconazole)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticide and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision, www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php#rrd) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act.*